Communication

Catalytic Direct Desaturation of Lactams Enabled by Soft Enolization

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Catalytic Direct Desaturation of Lactams Enabled by Soft Enolization

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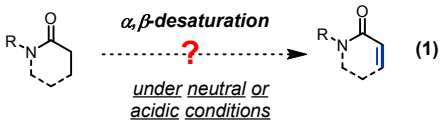
Supporting Information Placeholder

ABSTRACT: A direct and catalytic method is described for the α,β-desaturation of *N*-protected lactams to their conjugated unsaturated counterparts under mildly acidic conditions. The reaction is consistently operated at room temperature and tolerates a wide range of functional groups, showing complementary reactivity to the prior desaturation methods. Lactams with various ring sizes and substituents at different positions all reacted smoothly. Synthetic utility of this method is demonstrated in a concise synthesis of Rolipram. In addition, linear amides also prove to be competent substrates, and the phthaloyl protected product serves a convenient precursor to access various conjugated carboxylic acid derivatives. Strong bases are avoided in this desaturation approach, and the key is to merge soft enolization with a Pd-catalyzed oxidation process.

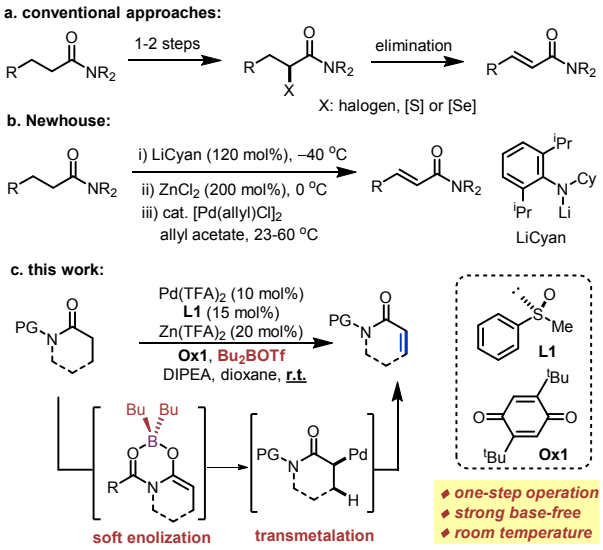
Lactams are prevalently found in biologically important compounds, such as natural products, pharmaceuticals and agrochemicals.[1] While methods to derivatize lactam α positions are well established through enolate chemistry, functionalization of the corresponding β position usually relies on conjugate addition of a soft nucleophile to an α,β-unsaturated lactam.[2] Undoubtedly, direct C−C bond formation at the β-positions of saturated lactams would be a more straightforward approach; however, it remains an unmet challenge due to the inertness and accessibility of the β-C−H bonds.[3] One potential solution would be a Pd-catalyzed redox-cascade strategy that was recently demonstrated to be successful for direct β-arylation of ketones with aryl electrophiles.[4] The catalytic cycle involves a Pd(II)-mediated ketone α,β-desaturation, a Pd(0)-mediated oxidative addition of Ar−I, migratory insertion of the resulting Pd(II)−Ar species to the enone intermediate and protonation of the Pd(II)-enolate by acids. However, implementing this strategy for lactam β-functionalization would require *a general amide desaturation method under neutral or acidic conditions* (Eq 1). To the best of our knowledge, such a transformation has not been realized previously, which became the motivation of this study.



(1)

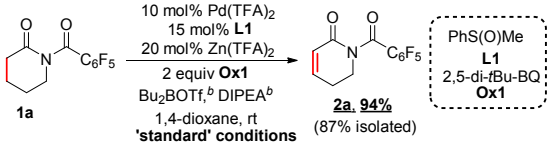
In contrast to various ketone desaturation approaches,[5,6] the corresponding transformations with amides are more difficult, primarily caused by the reduced acidity of their α-C−H bonds. Conventional approaches generally rely on introducing an α-leaving group, e.g. halogen, sulfur or selenium derivatives, followed by an elimination step (Scheme 1a).[7,8] While widely used, these methods demand multiple steps and/or use of strong bases. Alternatively, Pd-catalyzed Saegusa-type oxidation of amides is known, though silyl-enol ethers need to be formed in a separate step.[9] Very recently, Newhouse and coworkers developed a more direct approach for dehydrogenation of amides involving enolate formation with a novel lithium anilide, subsequent transmetalation to zinc and then Pd-catalyzed dehydrogenation with allyl acetate as an oxidant (Scheme 1b).[10] The necessity of strong bases for α-deprotonation and different reaction temperatures in each operation prevents this approach to be applicable in the proposed β-functionalization strategy. Herein, as an initial but important step towards the goal of enabling β-C−C forming reactions of lactams, we disclose a new direct method for desaturation of *N*-protected amides under acidic conditions. Remarkably, this approach can be operated in a single step consistently at room temperature without any strong bases.

Scheme 1. Desaturation of Amides.

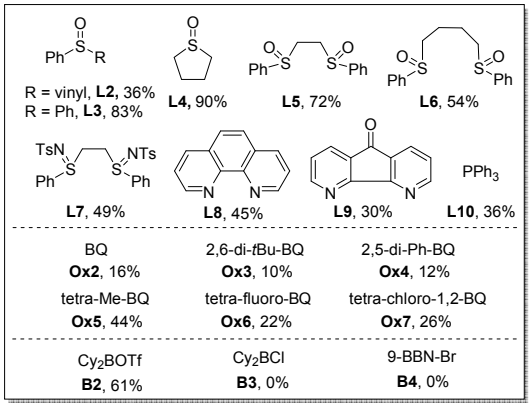


We conceived the approach of *merging "soft enolization"*[11] *with Pd-catalyzed enolate oxidation* to realize a strong-base-free lactam desaturation method. It is envisioned that, in the presence of a Lewis acid and a *weak base*, an amide enolate would be generated *in situ*, which can then undergo transmetalation to give a Pd(II) enolate. Subsequent β−H elimination would lead to α,β-unsaturated lactams (Scheme 1c). The active Pd(II) catalyst can be regenerated by an oxidant. *The merits of this lactam-desaturation approach are three-fold*: 1) soft enolization would avoid using strong bases; 2) cryogenic conditions would be unnecessary, allowing for a consistent reaction temperature; and 3) owing to a different mode of activation, a complementary substrate scope is expected compared to the known methods.

Table 1. Selected Optimization Studies[a]

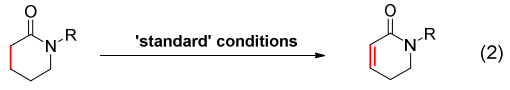


Entry	Variations from the 'standard' conditions	Yield (%) of **2a**[c]
1	Without **Pd(TFA)$_2$**	0
2	**L2-10** instead of **L1**	Listed below
3	Without **L1**	42
4	Without **Zn(TFA)$_2$**	40
5	**Ox2-7** instead of **Ox1**	Listed below
6	Without **Ox1**	6
7	**B2-B5** instead of **Bu$_2$BOTf**	Listed below
8	Without **Bu$_2$BOTf**	0
9	Without **DIPEA**	12
10	0.65 equiv **Bu$_2$BOTf** was used	50
11	0.65 equiv **DIPEA** was used	33
12	solvent = THF	18
13	solvent = toluene	0
14	solvent = MeCN	30
15	solvent = DCM	29



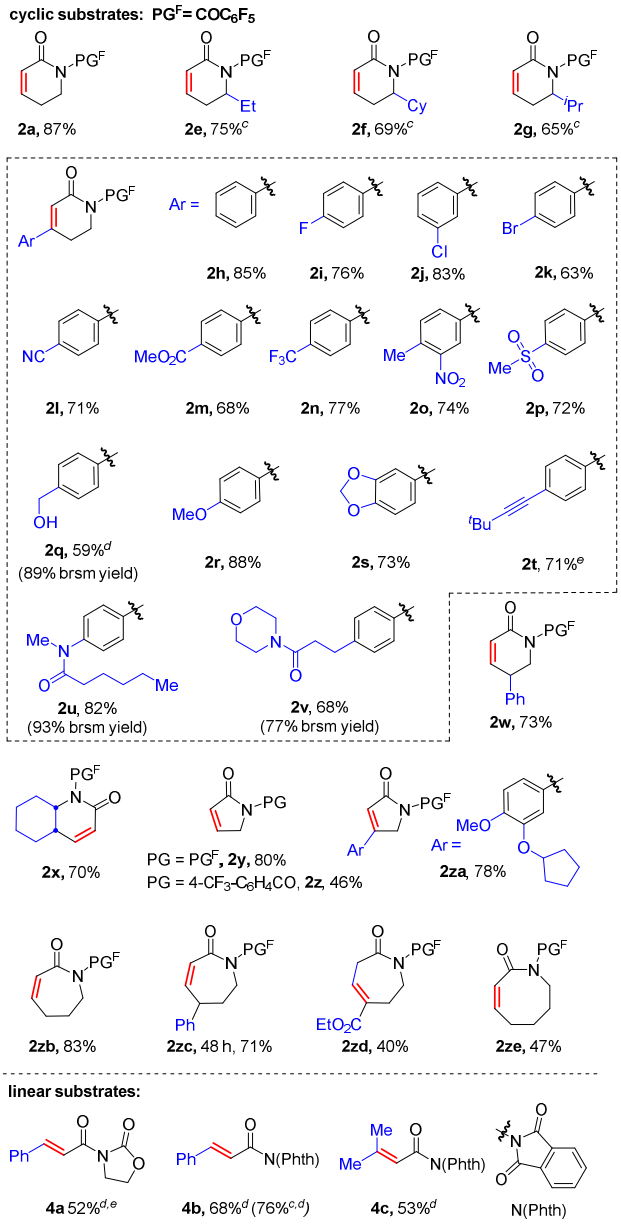
[a]Each reaction was run on a 0.1 mmol scale in a sealed 4 mL vial for 24 h. [b]1.3 equiv. [c]Yields were determined by ^{1}H NMR using CH_2Br_2 as the internal standard. TFA = trifluoroacetate.

Our study began with valeroalactam **1a** as a model substrate. After extensive optimization, the desired α,β-unsaturated lactam **2a** can ultimately be obtained in 94% yield at room temperature through a boron-enolate intermediate (Table 1).[12] The role of each reactant was then explored through control experiments. Clearly, the palladium catalyst is critical to this transformation, as no product was observed in the absence of Pd(TFA)$_2$ (entry 1). A range of phosphine, nitrogen and sulfur-based ligands have been examined, whereas the sulfoxide-type ligands are superior (entry 2). Interestingly, a 42% yield can still be obtained without any ligand (entry 3), and the role of the sulfoxide ligand is likely to stabilize the Pd catalyst.[6e] A catalytic amount of Zn(TFA)$_2$ significnatly enhanced the reaction efficiency (entry 4), which is likely due to an accelerated transmetaltion step.[13] The choice of the bulky 2,5-di-*t*-butyl-quinone oxidant (**Ox1**) is critical (entries 5 and 6), as other quinones gave much lower yields likely due to competing aldol-type reactions with the enone moiety of quinones. Note that using Cu(TFA)$_2$ as the oxidant instead only yielded the desired product in 20% yield. Bu$_2$BOTf/DIPEA is known to be an outstanding Lewis acid/base pair for soft enolization of ketones and *N*-acyl oxazolidinones;[14] however, its use to enolize lactams has not been reported. This Lewis pair turns out to be highly efficient for desaturation of lactam **1a**. Use of other Lewis acids or bases proved less efficient (entry 7 and see supporting information for more details), and the triflates anion appears to be important to enable chelation.[15] Attempts of using catalytic Bu$_2$BOTf or DIPEA remain unfruitful yet (entries 10 and 11). A survey of different solvents suggests 1,4-dioxane to be optimal (entries 12-15); in contract, the non-polar aromatic solvent, such as toluene, gave no desired product. It is worthy to note that pentafluorobenzoyl was found to be an excellent protecting group (PG), though other acyl PGs can also be employed (Eq 2).[16]



[a] Determined by ^{1}H NMR using CH_2Br_2 as the internal standard.
[b] Yield of isolated pure portion of the products. Complete separation from the lactam starting material is difficult.

Scheme 2. Substrate Scope[a,b]

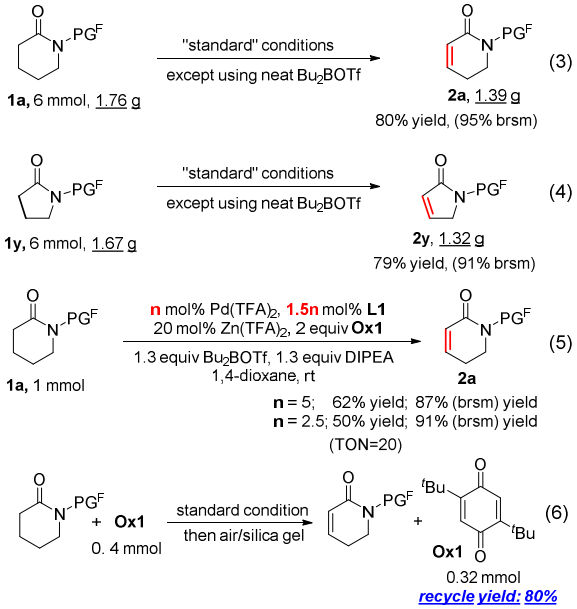


[a] Each reaction was run on a 0.2 mmol scale in a sealed 8 mL vial for 24 h. [b] All yields are isolated yields. [c] 20 mol% Pd(TFA)$_2$ and 30 mol% PhSOMe was used. [d] 2.6 equiv Bu$_2$BOTf and 2.6 equiv DIPEA was used. [e] Separation of the pure product from the start-

ing material was difficult. brsm: based on recovered starting material.

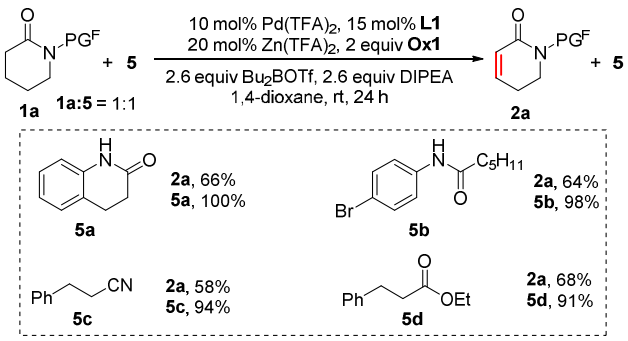
With the optimized conditions in hand, the substrate scope was next explored (Scheme 2). First, substitution at valeroalactam β,γ,δ-positions can all be tolerated (**2a-2w**). A higher catalyst loading is needed for substrates with a δ substituent (**2e-g**). Gratifyingly, a range of functional groups are compatible, such as aryl fluoride (**2i**), chloride (**2j**), bromide (**2k**), nitrile (**2l**), ester (**2m**), trifluoromethyl (**2n**), nitro (**2o**) and sulfone moieties (**2p**). In particular, unprotected benzyl alcohol (**2q**) and electron-rich aromatic rings (**2r** and **2s**), which are susceptible towards oxidation, remained intact. In addition, a relatively electron-rich alkynyl group (**2t**) is tolerated. When lactams **1u** and **1v** containing additional enolizable tertiary amides were employed as the substrate, the desaturation prefers to occur at the lactam moiety. Moreover, other types of lactams, including the one in a fused ring (**2x**), a number of five (**2y-za**), seven (**2zb-zd**) and eight-membered lactams (**2ze**), are competent substrates. Interestingly, for the seven-membered lactam substrate with a γ-ester group, the initially formed α,β-alkene isomerized to the β,γ-position during silica gel chromatography. Finally, although it is not the focus of this work, this desaturation protocol can also be applied to linear substrates. The oxazolidinone-derived amide afforded the desired product (**4a**) albeit in a moderate conversion. To our delight, phthalyl group was found to be an excellent PG for primary amides (*vide infra*, Scheme 4). Likely owing to the additional carbonyl moieties in the substrates, a higher loading of the Lewis acid was needed; nevertheless, the reaction proceeded smoothly for linear amides with mono and di-substitution at the β positions (**4b** and **4c**).

To test the practicality of this method, gram-scale reactions were carried out. On a 6.0 mmol scale the desired α,β-unsaturated lactams **2a** and **2y** were still isolated in 80% and 79% yields respectively with high mass balances (Eqs 3 and 4). In addition, when the catalyst loading was reduced to 5 and 2.5 mol%, although the conversions were moderate, up to 20 turnovers were obtained with excellent brsm yields (Eq 5). Furthermore, the benzoquinone oxidant (**Ox1**) can be easily recycled in a high yield upon treatment with air and silica gel[17] (Eq 6).



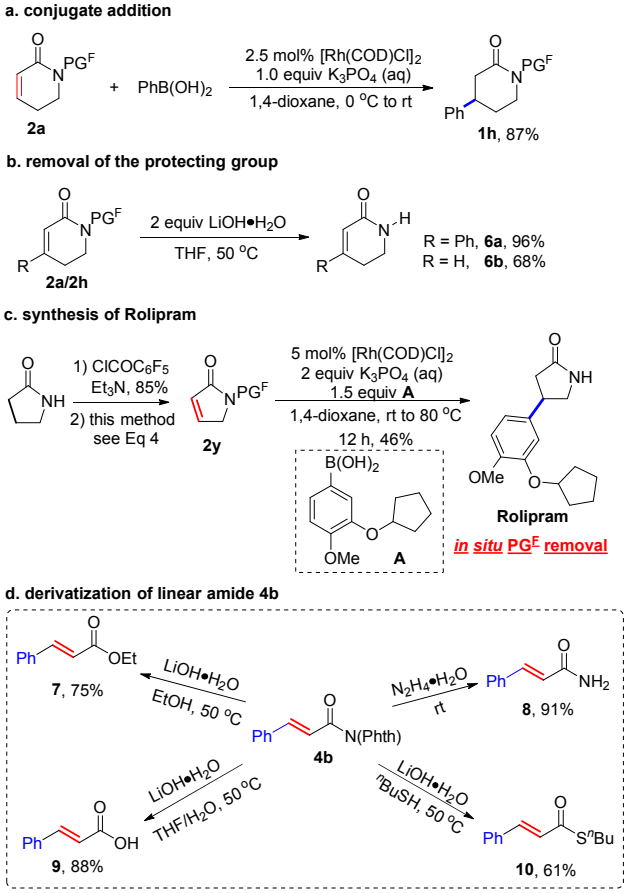
To further examine the chemoselectivity of this transformation, intermolecular competing experiments were performed between lactam **1a** and another desaturatable substrate (**5a-5d**). To our delight, dihydroquinolin **5a**, primary amide (**5b**), nitrile (**5c**) and ester (**5d**) were all found much less reactive than the *N*-protected lactam moiety, and can be recovered in more than 90% yields after 24 h. Note that desaturation of **5a** can be driven by forming a larger aromatic system; nitrile **5c** and ester **5d** are considered as excellent substrates using the prior dehydrogenation protocol.[18] Thus, this method exhibits complementary reactivity to the previous approaches. The observed high preference to desaturate the lactam group is likely due to the selective enolization caused by the strong chelation between the cationic boron Lewis acid and the 1,3-dicarbonyl moiety.

Scheme 3. Functional Group Compatibility Tests



To demonstrate the synthetic utility of this method, the α,β-unsaturated lactams can be easily derived through 1,4-addition of the phenylboronic acid via Rh-catalyzed conjugate addition (Scheme 4a).[19] The acyl PG^F can be easily removed under mild conditions with $LiOH•H_2O$ in THF at 50 °C to reveal free lactams (Scheme 4b).[20]

Scheme 4. Synthetic Applications



In addition, this method can be applied to enable a streamlined synthesis of Rolipram,[21] a potential drug for antidepressant and anti-Alzheimer's disease (Scheme 4c).[22] Gratifyingly, when the Rh-catalyzed arylation was performed at 80 °C, the PG^F group was surprisingly removed at the same time by aqueous K_3PO_4.

Thus, Rolipram is now made available in only three steps from inexpensive 2-pyrrolidinone.

Interestingly, *the phthalimide-protected amide was recognized as an underutilized surrogate for various carboxylic acid derivatives* (Scheme 4d).[23] For example, ester (**7**), free primary amide (**8**), carboxylic acid (**9**) and thioester (**10**)[24] can be efficiently obtained in a single step from linear conjugate amide **4b**.

In summary, as an essential step towards direct β-C−C-forming functionalization of lactams, we have developed an amide desaturation method that operates under acidic conditions at room temperature. The merge of soft enolization with palladium catalysis should have a broad implication on functionalization of other less enolizable carbonyl compounds. Detailed mechanistic studies through kinetic measurements and identification of key intermediates are ongoing to eventually enable using catalytic Lewis pairs. Development of direct β-arylation of lactams will be focused in the future work.

ASSOCIATED CONTENT

Supporting Information Experimental procedures; spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) (a) *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity*; Janecki, T., Ed.; Wiley-VCH: Weinheim, 2014. (b) Caruano, J.; Muccioli, G. G.; Robiette, R. *Org. Biomol. Chem*., **2016**, *14*, 10134.

(2) (a) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev*. **2003**, *103*, 2829. (c) Pineschi, M.; Moro, F. D.; Gini, F.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2004**, 1244. (d) Cottet, P.; Müller, D.; Alexakis, A. *Org. Lett.* **2013**, *15*, 828-831. (e) Yasukawa, T.; Saito, Y.; Miyamura, H.; Kobayashi, S. *Angew. Chem. Int. Ed*. **2016**, *55*, 8058.

(3) For a recent review on direct β C-C forming functionalization of carbonyl compounds, see: Huang, Z. X.; Dong, G. B. *Tetrahedron Lett.* **2014**, *55*, 5869.

(4) (a) Huang, Z. X.; Dong, G. B. *J. Am. Chem. Soc*. **2013**, *135*, 17747. b) Huang, Z. X.; Sam, Q. P.; Dong, G. B. *Chem. Sci.* **2015**, *6*, 5491.

(5) For representative reviews, see: (a) Ito, Y.; Hirao, T.; Saegusa, T., *J. Org. Chem.* **1978**, *43*, 1011; (b) Muzart, J. *Eur. J. Org. Chem.* **2010**, 3779. (c) Diao, T. N.; Stahl, S. S. *Compr. Org. Synth*. **2014**, *7*, 178. (d) Iosub, A. V.; Stahl, S. S. *ACS Catal.* **2016**, *6*, 8201.

(6) For seminal works on Pd-catalyzed ketone dehydrogenation, see: (a) Theissen, R. J., *J. Org. Chem.* **1971**, *36*, 752. (b) Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011. (c) Diao, T. N.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566. (d) Diao, T. N.; Wadzinski, T. J.; Stahl, S. S. *Chem. Sci.* **2012**, *3*, 887. (e) Diao, T. N.; Pun, D.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 8205.

(7) (a) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (b) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. (c) King, A. O.; Anderson, R. K.; Shuman, R. F.; Karady, S.; Abramson, N. L.; Douglas, A. W. *J. Org. Chem.* **1993**, *58*, 3384. (d) Matsuo, J.-i.; Aizawa, Y. *Tetrahedron. Lett.* **2005**, *46*, 407.

(8) For DDQ-mediated desaturation of γ,γ-dialkylsubstituted lactams, see: Bhattacharya, A.; DiMichele, L. M.; Dolling, U-H.; Douglas, A. W.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 3318.

(9) Weber, B.; Scharer, N.; Muller, B. W. U.S. Patent App 2006/0281949 A1, Dec 14, **2006**.

(10) Chen, Y. F.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2016**, *138*, 1166.

(11) For seminal discoveries, see: (a) Lehnert, W. *Tetrahedron Lett.* **1970**, *11*, 4723. (b) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559. (c) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(12) When this manuscript was in preparation, a ketone dehydrogenation method through a stepwise generation of boron enolates was reported, see: Sakamoto, Y.; Amaya, T.; Suzuki, T.; Hirao, T. *Chem. Eur. J.* **2016**, *22*, 18686.

(13) (a) Hama T.; Liu, X. X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc*. **2003**, *125*, 11176. (b) Liu, X. X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5182.

(14) Abiko, A. In *Boron Enolate Chemistry*; Coca, A., Eds.; *Boron Reagents in Synthesis*; American Chemical Society: **2016**, *1236*, 123-171.

(15) Use of $B(C_6F_5)_3$ has also been attempted. For a recent elegant work on using catalytic $B(C_6F_5)_3$ to enolize a range of carbonyl compounds for enantioselective α-amination, see: Shang, M.; Wang, X.; Koo, S. M.; Youn, J.; Chan, J. Z.; Yao, W.; Hastings, B. T.; Wasa, M. *J. Am. Chem. Soc*. **2017**, *139*, 95.

(16) Use of Ac as the PG gave a complex reaction mixture, likely due to a competing enolization on the Ac methyl group. Use of Ts as the PG gave no conversion of the lactam, likely due to the weak chelation effect of the sulfonyl group.

(17) Voleva, V. B.; Prokofeva, T. I.; Belostotskaya, I. S.; Komissarova, N. L.; Ershov, V. V. *Russian Chem. Bull.* **1998**, *47*, 1952.

(18) Chen, Y. F.; Turlik, A.; Newhouse, T. R. *J. Am. Chem. Soc.* **2015**, *137*, 5875.

(19) Takaya, Y.; Ogasawara, M.; Hayashi, T.; *J. Am. Chem. Soc*. **1998**, *120*, 5579.

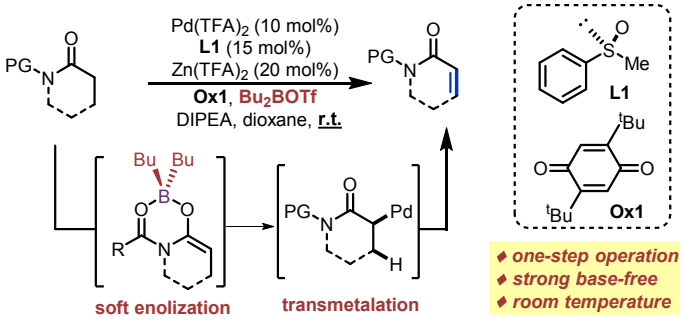
(20) Behenna, D. C.; Liu, Y. Y.; Yurino, T.; Kim, J. M.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nature. Chem*. **2012**, *4*, 130.

(21) (a) Lowe, J. A. L.; Archer, R. L.; Chapin, D. S.; Cheng, J. B.; Helweg, D.; Johnson, J. L.; Koe, B. K.; Lebel, L. A.; Moore, P. F.; Nielsen, J. A.; Russo, L. L.; Shirley, J. T. *J. Med. Chem*. **1991**, *34*, 624. (b) Myeku, N.; Clelland, C. L.; Emrani, S.; Kukushkin, N. V.; Yu, W. H.; Goldberg, A.; Duff, K. E. *Nat. Med.* **2016**, *22*, 46.

(22) For the previous syntheses, see: (a) Langlois, N.; Wang, H-S. *Synth. Commun.* **1997**, *27*, 3133. (b) Garcia, A. L. L.; Carpes, M. J. S.; Oca, A. C. B. M.; Santos, M. A. G.; Santana, C. C.; Correia, C. R. D. *J. Org. Chem*. **2005**, *70*, 1050. (c) Tonogaki, K.; Itami, K.; Yoshida, J-I. *J. Am. Chem. Soc*. **2006**, *128*, 1464. (d) Shao, C.; Yu, H-J.; Wu, N-Y.; Tian, P.; Wang, R.; Feng, C-G.; Lin, G-Q. *Org. Lett.* **2011**, *13*, 788. (e) Yang, X-F.; Ding, C-H.; Li, X-H.; Huang, J-Q.; Hou, X-L.; Dai, L-X.; Wang, P-J. *J. Org. Chem*. **2012**, *77*, 8980. (f) Schmidt, B.; Elizarov, N.; Berger, R.; Petersen, M. H. *Synthesis* **2013**, *45*, 1174. (g) Ghislieri, D.; Gilmore, K.; Seeberger, P. H. *Angew. Chem. Int. Ed*. **2015**, *54*, 678. (h) Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329.

(23) Rabjohn, N.; Drumm, M. F.; Elliott, R. L. *J. Am. Chem. Soc*. **1956**, *78*, 1631-1634.

(24) A thiol conjugate addition product (28% yield) was also isolated.


Pd(TFA)2 (10 mol%)
L1 (15 mol%)
Zn(TFA)2 (20 mol%)
Ox1, Bu2BOTf
DIPEA, dioxane, r.t.
PG
N
O
Bu Bu
B
R
soft enolization
Pd
H
transmetalation
S
Me
L1
tBu
Ox1
one-step operation
strong base-free
room temperature